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ECTOPIA OF THE ADRENAL.

By Henry E. Radasch, M.D.,
DEMONSTRATOR OF EMBRYOLOGY AND HISTOLOGY IN THE JEFFERSON MEDICAL COLLEGE.
(From the Laboratories of the Jefferson Medical College.)

The object of this paper is to give a brief résumé of the cases on record and a short sketch of the histology and embryology of this gland so far as they bear upon ectopia of the organ.

Histologically, the adrenal is composed of cortex and medulla, the former consisting of zona glomerulosa, zona fasciculata, and zona reticularis. The capsule surrounding the organ is composed of elastica in the outer part and white fibrous connective tissue in the deeper portion. In the latter Joesten and Rauber found involuntary, non-striated muscle fibres. Besides these, bloodvessels, nerves, ganglia, accessory adrenals, and bands of cells of the zona glomerulosa are also found. The capsule does not strip and is thinner in children than in adults. In the outer part of the zona glomerulosa the cell groups are elongated, while in the lower part they are globular. These cell groups are surrounded by connective tissue and capillaries. The nuclei are large and the protoplasm of the peripheral cells less in amount than that of the deeper cells. Extra nuclei are sometimes found in these cells. This zone is quite irregular, and in children may even be wanting. The cells of the zona fasciculata are arranged in strands or columns between which are found the connective tissue, bloodvessels, and lymphatics. The cells are more regular and paler than those of the preceding zone and stain less readily. They contain, except in children, fat globules. The nuclei are smaller, granular, and situated in that part of the cell nearest the capillaries. There are usually, in these columns, two cells side by side. In the deeper layers of this zone the cells are less sharply defined and the nuclei central. The zona reticularis consists of cells arranged in a network, the continuation of the columns of the zona fasciculata. The cells are small, nuclei large, and the protoplasm pigmented with a yellowish-brown substance. In old age this zone is irregular, and in places wanting.

The medulla is separated from the above by a layer of large, smooth cells. It contains a network of connective tissue bundles, within the meshes of which are fragmented chains or groups of cells which stain deeply with chromium compounds. The nuclei are large, and often there is but little protoplasm.

Nerves and ganglion cells are abundant. The vessels are numerous and large, especially the veins. The adrenals of the newborn and young children are rich in furrows. This is of importance in the formation of accessory adrenals. In youth and adult life they are smooth.

Reviewing briefly the embryology of the adrenal we find that it has a double origin. According to Hertwig,[1] Balfour, Braun, Kölliker, and Mitsukuri, the medulla is derived from ganglionic outgrowths of the sympathetic system. The cortex, however, has a greatly disputed origin. Balfour, Braun, and Mitsukuri hold that it is developed from mesodermic cells just anterior to the mesonephros in a concavity of the cardinal vein. Hertwig, Minot, Janosik, Weldon, Milhalkovics, Semon, Hoffman, and Hans Rabl consider it of epithelial origin. Janoski and Milhalkovics hold that it is developed from the head end of the genital ridge, or epithelial cells in that region, while Weldon, Hertwig, and Minot believe that it arises from the head end of the mesonephros. (See also Aichel.[11]) The cortex as it develops surrounds the medulla and finally almost completely encloses it.

According to Chiari[2] the adrenal is developed from the peritoneal cells at the head end of the sexual gland anlage. As it consists of the same tissue as the latter it remains in intimate relation with it until the development of bloodvessels and the permanent kidney breaks up this relationship. At or about this time small parts or collections of cells may become detached, such fragments or even the whole gland becoming ectopic structures.

In an embryo of the second or third month the adrenals lie in close proximity to the inferior vena cava. Later, with the descent of the testis or ovary, small cell-groups or detached portions of the developing organ may be drawn away from their former positions and deposited at various places along the path of descent of the developing organs and especially through the necessary lengthening of the spermatic veins.

At this time the adrenals are comparatively large, enclosing nearly the whole kidney. The two are separated by connective tissue, the future capsule of the kidney. As the kidney is lobulated in the fœtal condition it is easy to understand how small detachments of cells could be enclosed in the interlobular connective tissue at this stage, and so account for the presence of adrenal tissue in the columns of Bertini and other parts of the adult kidney.

Mention of accessory or misplaced adrenal occurs as early as 1568, followed by that of Morgagni, in 1740, and Duvernay, in 1751. Rokitansky found bodies of various sizes in the region of or upon the normal adrenals, in the solar and renal plexuses, and even the cortex and medulla of the adrenal body itself. Klebs, in 1876, states that, in addition to the above places, accessory organs may be found upon the kidney, beneath the capsule, and even within the kidney substance itself. Since then such structures have been found in the region of the internal abdominal ring, in the inguinal canal, upon the spermatic cord, between the epididymis and testicle, in the broad ligament, and in structures neighboring to those mentioned. They have also been found in the liver and within the capsule of the adrenal.

Marchand,[3] in his article of 1883, was the first to give a detailed description of these bodies. All his cases occurred in infants and children, and from this he drew the conclusion that in youth they disappeared and so were not met with in adult life. In his cases the bodies occurred in the broad ligament and in the region of the kidney.

In the first case the main body was found in the broad ligament, and smaller ones in the right adrenal. On section the larger one exhibited the cortex only.

The second, third, and fourth cases showed the accessory bodies in the broad ligament. The second one, on section, showed a yellowish-white edge and a yellowish-gray centre. It was, according to his conclusions, the only one to be found that exhibited anything like a true medulla. Its cortical cells contained fat globules. The other two were practically the same as case one.

The fifth case exhibited a small body just behind the right kidney.

The sixth case showed a number of small ball-like masses on the kidney and to the median side of the adrenal. On section these showed only cortex.

The fallacy of Marchand's conclusion, that accessory adrenals were to be found in children only, was soon proven by the findings of Schmorl.[4] His cases were adults, and he found a wider distribution of the accessory structures.

His first case, a man, aged thirty years, exhibited a small body just outside of the external abdominal ring. It lay upon the spermatic cord in close relation to the artery and the vein. It was yellowish-brown, smooth, pea-sized, and upon section showed a peripheral zone and a grayish-white centrum. In the latter the lumina of many small vessels were to be seen. The cortex showed adrenal substance, while the medulla consisted of delicate connective tissue and many bloodvessels.

D'Ajutolo[5] found such a body on each spermatic cord, just within the internal ring, of a newborn infant. In Schmorl's second case he found a small mass 2.5 mm. by 1.5 mm. in the right lobe of the liver. This was sharply defined and consisted of a dark yellow periphery and a brownish, not well-defined centrum. The cortical cells were in groups surrounded by delicate connective tissue and thin-walled bloodvessels. The zona fasciculata showed fat globules and in some cells yellow pigment. In a woman, aged thirty years, he found three small bodies in the liver, and in another case two in the right lobe. In his next case the accessory adrenal structure occurred (in the liver) as a well-defined mass, about the size of a hazelnut. The cell protoplasm was pigmented, while some of the columns of cells showed hyaline degeneration. The centrum contained many bloodvessels.

The liver, no doubt, makes an effort to dispose of these foreign cells, and in some cases is successful, while in others the cells persist, multiply, become encapsulated and produce masses such as that just mentioned. (See also Noyes.[11])

Schmorl demonstrated a wide distribution of ectopic adrenals and also that such malposition occurred in adults, both male and female. Chiari,[3] in 1884, reported several cases. In his first case a small body was found posterior to the right kidney. It was about the size of a pea, yellowish-brown in color, and on section showed only cortex. The centrum consisted of bloodvessels and delicate connective tissue, and just external to these structures pigment cells were noted. Beyond this was the rest of the cortex. All three zones were distinct and all contained fat, the zona glomerulosa being richest in this element.

The second occurred in the broad ligament of a woman. Here the pigment zone was well marked, and the centrum especially so. The cells of the zona reticularis were pigmented and the whole mass encapsulated.

The third showed a small mass beneath the right kidney, near the adrenal, and the fourth also beneath the right kidney. Here the general characteristics were the same.

Ulrich[4] reported an adrenal in the kidney, another upon the upper pole of the right kidney, separated from the renal tissues by the capsule of the kidney. The same observer noted two other instances, both in children, one fourteen days and the other three years old. His third case showed all three zones, no medulla, no fat, and no pigment.

Dagonet's[7] first case showed a pea-sized body in the broad ligament just below the ovary. In the second there were two, one lying between the testicle and epididymis, and another on the spermatic cord. Of these the first showed the zona glomerulosa and zona fasciculata and a centrum rich in capillary bloodvessels. The cell stained deeply, but contained neither fat nor pigment. He made the observation that in children the centrum was red and the vessels filled with blood, while in the adult the centrum was usually pigmented and dark.

Kelly[8] reported a case in which there was union of the adrenal and kidney and a displaced mass of the former, irregular in shape, in the cortex of the latter. The little adrenal islets had portions of kidney cortex enclosed within them. Besides these, there are the cases of Rossa (quoted by Warthin[15]), four in the broad ligament, and of these two in newborn children; those of Meyer, seven in children and fœtuses; and

Gottschalk's, one in an adult. Wahneau reported a case in which an ectopic adrenal was found in the cœliac ganglion.

The occurrence of ectopic adrenals is not so infrequent as might be supposed. Imbert[9] states that they occur in about 92 per cent. of all autopsies, and they are found in the kidney in 6 per cent. to 8 per cent. of cases. Eastwood[10] calls attention to the malignancy of the neoplasms, developing from adrenal rests. His paper takes up those occurring in the pelvis in connection with the spermatic and ovarian veins and broad ligament. He found a large malignant tumor in the fundus uteri. It consisted of a large, encapsulated mass the cells of which resembled those of the zona glomerulosa. Imbert[9] experimented on dogs with the view of producing tumors composed of adrenal tissue. He detached the left adrenal and inserted it into a longitudinal incision in the kidney, and studied the results in the animals that recovered. In one dog three and a half months after operation the tumor resembled the so-called pseudolipoma of the kidney. He considers this an experimental pseudolipoma of the kidney. In another case he produced a cystic condition.

The importance of ectopic adrenals is not their frequency, but the frequency with which they give rise to neoplasms. Their importance is being more fully realized as tumors supposed to be lipomas and adenomas are found to consist, histologically, of adrenal rests.

Grawitz[11] first directed attention to the fact that certain tumors of the kidney were composed of adrenal tissue, adrenal rests, and Kelly[8] in an exhaustive review of hypernephromas has fully summed up the various views as to their origin and general character.

Ectopic adrenals respond to the following tests:

1. *Histological.* The peculiar, indeed, quite characteristic architecture of the organ as a whole as well as its component layers.

2. *Chemical.* Gives the reaction for glycogen. The specific brown coloration in chromium fixed preparations, said by Böhm and Davidoff not to be observed elsewhere except in certain cells of the hypophysis.

3. Presence of fat globules in the cells, especially in the zona glomerulosa.

4. *Staining reaction.* By the use of Weigert's fibrin and Russel-fuchsin stains, Lubarsch[11] found that the nucleus and nucleolus of adrenal cells stain differently. No other tissue responds to this test.

After this brief résumé of the occurrence of accessory adrenals and the histology and embryology of the normal gland, I desire to report the following case:

The patient,* J. L., male, aged twenty-nine years, was admitted to the Jefferson Medical College Hospital, the diagnosis being gumma or tumor of the brain; although the previous history yielded no satisfactory data, it was believed that the lesion was syphilitic. Had recurring convulsions that at the time of admission were uncontrolled by usual remedies, and occurred every fifteen minutes. He was trephined for the purpose of reducing pressure and as an exploratory procedure. Death occurred on the following day.

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* For this brief abstract of the history the writer is indebted to Dr. Spencer. Other features of the case will be reported elsewhere.

Autopsy by Prof. Coplin, to whom the writer is indebted for the use of the autopsy record, the material, and suggestions in the preparation of this report.

Pathological Diagnosis. Numerous hemorrhages in subcutaneous fat, spleen, and subserous tissues; cloudy swelling in the heart, liver, and kidneys. Hypostatic congestion and pulmonary œdema; lobular atelectasis. Ectopic of adrenal; intense meningeal congestion; gumma in left frontal lobe.

Only so far as bearing upon the matter at hand, will it be necessary to give a summary of the autopsy notes.

The kidneys were about normal in size, but somewhat flabby. Internally they showed but little abnormality. Upon the anterior superior surfaces of both kidneys a thin yellowish body was noticed. This covered an irregular area about 3 cm. in diameter, and approximately 1 mm. thick. The peripheral portion was yellowish, while that toward the cortex of the kidney was dark. They were beneath the capsule in each instance, and in places dipped into the cortex. One adrenal of normal shape, size, and location was present on the right side.

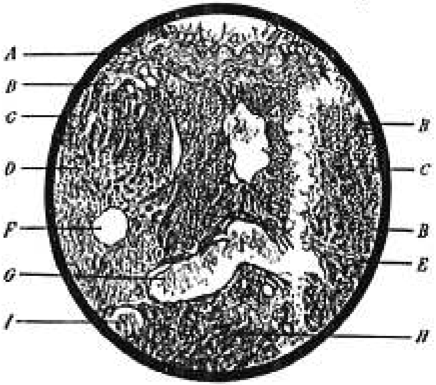
Upon the under surface of the liver near the transverse fissure, a small, thin mass was noticed. It resembled that upon the kidney. It was approximately 1 cm. in diameter and 0.2 cm. thick, tapering at the ends like a small adrenal. Upon section it had the appearance of normal adrenal tissue. Pieces of these masses were placed in Heidenhain's solution and Müller's fluid, dehydrated in ascending strengths of alcohol, cleared in turpentine, and embedded in paraffin.

Adrenal in the kidney. (See Fig. 1.) Upon histological examination the adrenal, in connection with the kidney, showed the following structure: The capsule was rather thick and composed of white fibrous connective tissue. In the deeper layers were apparently some involuntary nonstriated muscle fibres. Between the groups of cells of the zona glomerulosa and capsule were many red blood cells. These were also noticed scattered between the glomeruli. The groups of cells of this zone were large and small; in places these were wanting, the zona fasciculata reaching nearly to the capsule. In others the glomerular zone was five or six groups deep. The edge of this patch of adrenal tissue tapered, and at the extreme margin the capsule was seen separating it from the kidney cortex, but for only a short distance. Here the zona glomerulosa followed the capsule to its end. Over this area the regular capsule was quite thick and apparently laminated. Between the lower layers were extensive but narrow spaces containing large numbers of red blood cells. Beyond the area of true adrenal tissue this capsule extended as a thick mass of connective tissue in which were great numbers of erythrocytes. Here also were found fat and elastic tissue, the latter continued from over the area of adrenal substance. Within the capsule were also groups of cells resembling those of the zona glomerulosa and separate cells, which took the nuclear stain quite deeply. These latter cells were arranged in a band in the middle of the capsule, and as the adrenal substance was reached the band became broader and ended abruptly.

At one place a beam of tissue, apparently involuntary non-striated muscle fibre at its inner end, passed in at an acute angle, cutting off a triangular portion of the adrenal cortex. Large and small bloodvessels were present in abundance and nearly all filled with blood cells.

Just beneath the capsule was a single row of cells that extended quite a distance. They appeared the same as the rest of the cells of the zona glomerulosa. Beneath this the groups were large and irregular. The number varied from two to six in depth. The cells and nuclei of those nearer the capsule were small, with outlines usually indistinct. Most of the remaining nuclei, however, were large and prominent and took all stains deeply. They were circular in outline and mostly eccentrically placed. The nuclear membrane was sharply outlined, and in those cells less deeply stained the nuclear fibrils were seen in various arrangements, apparently karyokinetic figures. The nuclei vareid from six to thirteen microns in diameter, the average being about eight to nine. The cell protoplasm stained but faintly and irregularly, giving the appearance of fat globules. The outlines were usually indistinct, and the diameter varied from eighteen to thirty microns. A few had two or three nuclei. Between the groups, beneath the capsule, were noticed red blood cells scattered and grouped.

FIG. 1.

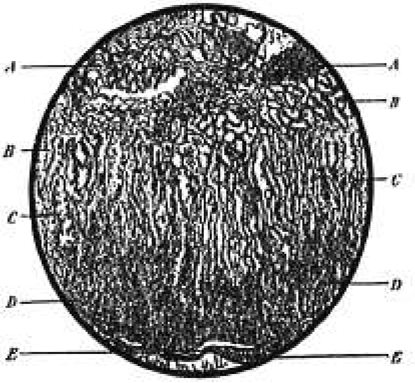


Section of cortex of kidney containing ectopic adrenal. (Fixed in Heidenhain's solution; paraffin, hæmatoxylin, and Van Gieson. Obj. 16 mm., oc. compensation, and reduced ½.) *A.* Capsule of kidney extending over adrenal. *BBB.* Zona glomerulosa. *CC.* Zona fasciculata. *D.* Zona reticularis. *E.* Capsule projected between adrenal and kidney cortex partly separating the two structures. *F.* Cavity surrounded by Bowman's capsule, external to which is adrenal tissue. *G.* Large vein. *H.* Kidney cortex. *I.* Imperfectly developed Malpighian body.

Zona fasciculata. The columns were long and parallel as in the normal structure, and separated by connective tissue. The cells were larger than those of the zona glomerulosa, and the nuclei averaged ten to twelve microns in diameter. These were placed eccentrically toward the centre of the columns and showed karyokinetic figures. The protoplasm stained more deeply and more regularly than in the above zone, and the cell outline was also more distinct. The cells in the lower portion of this zone were of a peculiar olive-green color, the nuclei deeply stained, and the whole somewhat hazy.

Zona reticularis. Here the cells were smaller and the nuclei comparatively large, averaging ten microns. Frequently two were seen in a single cell. The nuclei were irregularly placed; no matter what stain was used the cells were of a peculiar olive-green color and somewhat hazy. They were indiscriminately scattered and not arranged in definite chains, groups, or network. The cell outlines were more distinct than in the other zone. Some of the nuclei were quite distinct, showing peculiarities of those of the other zones. Here also a great many red blood cells were noticed scattered and in groups. A number of tubules, about eleven, were noticed here. These were lined by simple squamous epithelial cells and two contained imperfect Malpighian bodies. This zone passed directly into the cortex of the kidney, except at the outer edges of the patch. At this portion the zona reticularis was absent. Between this zone and the cortex at places larger spaces were visible, apparently cystic in character, perhaps greatly distended capsules of Bowman, as they were lined by simple squamous epithelial cells.

FIG. 2.



Section of ectopic adrenal beneath the peritoneum and intimately attached to the capsule of the liver. *A A.* Capsule of Glisson. *B B.* Zona glomerulosa. *C C.* Zona fasciculata. *D D.* Zona reticularis. *E E.* Peritoneal surface.

Mass under the liver. (See Fig. 2.) Here apparently the order of the zones was reversed. Separating this mass from the liver was a thick layer of loosely arranged connective tissue containing oval masses of cells apparently adrenal glomeruli, pigmented as those of the zona reticularis.

The zona glomerulosa was only two or three cell groups in depth. The cells were smaller than those in the foregoing specimen and stained more deeply. The nuclei averaged nine to ten microns, were eccentrically placed, and stained intensely. Blood cells were found between the groups. In the zona fasciculata the cells were also smaller than those in the kidney, but the nuclei were larger. The latter averaged twelve to fourteen microns, were eccentrically placed, and stained deeply. The cells were darker than those of the third zone. The columns were quite long and well separated in places. The zona reticularis stained well, the nuclei were prominent, and the cell protoplasm was less hazy than in the kidney specimen. The cells were as large as those in the zona reticularis of the above, but deeper in color, containing, apparently, more pigment. The network was closely meshed, especially in the deepest part, where the cells formed an almost solid mass the extent of the section. Here the color was an olive-green.

Over the greater extent of this mass was a band of tissue, apparently representing the peritoneum. In places the strands of this tissue were separated, and the spaces contained an abundance of red blood cells. For quite a distance it gave way to several layers of large polygonal epithelial cells. The nuclei were prominent and eccentrically placed, but the cell walls were indistinct. The cells were deeply colored, like those of the zona reticularis, but separated from them by connective tissue and bloodvessels in places.

From the above it will be seen that the zona reticularis was external, a very unusual condition.

CONCLUSIONS. 1. Ectopic adrenals are found in both sexes and all ages. 2. Their occurrence is far more frequent than formerly supposed. 3. Although they vary in size, most of them conform to the general description of yellowish, oval, or globular bodies, which on section show a light periphery and a dark centrum. 4. Microscopically these bodies consist of two or three zones of the cortex of the adrenal, but seldom of the medulla. (Marchand's second case was the only exception, and no complete histological description was given.) May,[14] however, found both cortex and medulla in two out of ten of his cases. 5. The separation of the masses occurs early, before the inclusion of the medulla by the cortex of the normal gland. 6. The distribution varies greatly, the usual location being some point between the kidney and the descended sexual gland; to this is to be added the unusual location, the under surface of the liver, and also within the organ.

NOTE.—While this paper has been in the hands of the printer, Joseph C. Ohlmacher (*Journal of Medical Research*, May, 1902, vol. vii. No. 4, p. 421) has reported a malignant medullary hypernephroma of the kidney.

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A CASE OF HEMORRHAGIC EXUDATIVE ERYTHEMA (HENOCH'S PURPURA).[1]

By Herbert Swift Carter, M.D.,
of New York City.

The case here presented is one of a modified form of Henoch's purpura, in which the abdominal symptoms were as severe as they were interesting.

The entire subject of the etiology of most of the purpuric conditions is so hopelessly obscure at the present time that no discussion of it will be attempted. Whether in this or in other cases it is due to changes in the blood cells, plasma reaction, coagulability, or the presence of the ever possible toxins in it, derived from uneliminated excrementitious matter, is simply a matter of speculation, there being nothing positive in this instance to point to, the intestinal canal, however, not being above suspicion.

History. Mrs. S., American, aged twenty-nine years.

Family History. Her sister has had attacks of what has been called "gastric neuralgia," characterized by very severe abdominal pain (not associated with an eruption), lasting from a few hours to the greater part of the day; often associated with obstinate constipation. The mother also suffers from facial neuralgia.

Previous History. As a child she had a very severe attack of measles. She has never had rheumatism in any of its regular manifestations. Not alcoholic. No menstrual irregularities. She has always been an exceedingly healthy woman, with no hæmophilic tendency whatever.

Present Illness. On March 6th the patient had a late supper consisting of sweetbreads and coffee. The following evening she complained of a moderate sore-throat, and noticed a few scattered, bright red spots about both elbows. There had been considerable constipation for several days previously. As she felt perfectly well otherwise, no attention was paid to the spots until the next day, when it was noted that the eruption was more profuse, and had appeared on the legs above the ankles. She was seen first on March 9th by the writer, and the following notes taken:

Physical Examination. At 10 A.M. temperature was 98.6° F.; pulse, 84; respirations, 20. The patient is slightly anæmic. Tongue moist and very slightly coated. No enlargement of superficial glands.

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[1] Read before the New York Society of Internal Medicine, April meeting, 1902.